REMARKS

Status of the Claims

Claims 23, 25-28, 30-34, 36 and 38-56 are in the application.

Claims 23, 25-28, 30-34, 36 and 38-56 are rejected.

By way of this Amendment, claims 23, 25, 30-32, 36, 39, 42, 43, 45, 48 and 50 have been amended, claims 28 and 49 have been canceled, and new claims 57-61 have been added.

Upon entry of this Amendment, claims 23, 25-27, 30-34, 36, 38-48 and 50-61 will be pending.

Summary of the Amendment

The claims have been amended to more clearly define embodiments of the invention.

Claims 23, 25, 32, 42, 43, 45, 48 and 50 have been amended to more clearly set forth that the ST receptor ligand is an antibody that binds to ST receptor, an antibody fragment that binds to ST receptor or a peptide that binds to ST receptor. The language has been amended to reflect proper Markush form. No new matter has been added.

Claims 25, 32, 43, 45 and 50 have also been amended to more clearly set forth that the fragments and derivatives of the specific peptides referred to therein which are within the scope of the claims each binds to ST receptor. No new matter has been added.

Claim 28 has been canceled as not further limiting claim 23 are amended by way of the previously filed amendment.

Claims 30-32, 36 and 39 have also been amended to more clearly and consistently refer to the non-peptide radiostable therapeutic agent as referred to in claim 23. No new matter has been added.

Claim 48 has been amended to incorporate the limitation of claim 49 and to more clearly set forth the subject matter of the claim. No new matter has been added.

Claim 49 has been canceled in view of the amendment to claim 48.

New claims 57 and 58 has been added to more specifically define embodiments of the invention. No new matter has been added.

New claims 59-61 has been added to specifically refer to methods of treating individuals who have colorectal cancer. New claims 59-61 correspond to claim 21 as originally filed and further correspond to specific compositions of matter in the current claim set. No new matter has been added.

The claims as amended and new claims all read on the elected invention and species except new claims 59-61 which read on non-elected Group V.

Rejection under 35 U.S.C. §112, first paragraph

Written Description Rejection

Claims 23, 25-28, 30-34, 36 and 38-56 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement. The Official Action states on page 10 that

> [c]laims 23, 42 and 48 are drawn to a genus of "pharmaceutical compositions" comprising a genus of ST receptor binding ligand, and a genus of active (or therapeutic) agent. Neither the instant specification nor the claims have demonstrated common structure and/or function for the claimed genus of "pharmaceutical compositions" comprising various ST receptor binding ligands, and active agents. In addition, no representative number of species for each claimed genus is provided to show possession of the claimed genus of "pharmaceutical compositions" for using to treat various diseases. That is the claimed "pharmaceutical composition" can comprise any ST receptor binding ligand (i.e. any peptide, any antibody, and fragments thereof) and any active agent that can be any molecules. (*sic*)

It is further asserted in the Official Action that the "only examples of "pharmaceutical compositions" (Official Action at page 10) disclosed in the specification are disclosed at pages 36-44 and 72-75, and that the term "fragments" is broad and encompasses almost any number of amino acids which when formulated "may or may not exhibit the desired pharmaceutical effects." (Official Action at page 11).

Applicant respectfully urges that the application is in all respects in compliance with the written description requirement of the first paragraph of 35 U.S.C. 112, and that the specification provides clear evidence that Applicant was in possession of the claimed invention at the time the application was filed.

In view of the amendment of the claims, it is clear that the ST receptor ligand, whether an antibody, a fragment of an antibody or a peptide binds to ST receptor. Claims 23, 25, 32, 42, 43, 45, 48 and 50 have been amended to specifically recite that the ST receptor ligand is selected from the group of antibodies that bind to ST receptor, antibody fragments that bind to ST receptor and peptides that bind to ST receptor. Claims 25, 32, 43, 45 and 50 have been amended to specifically recite that the fragments and derivatives of peptides having the specifically referenced sequences in claims "bind to ST receptor."

Regarding claims 23, 42 and 48, contrary to the assertions in the Official Action, the specification and claims clearly demonstrate that the claimed genus has a common structure and function. Claim 23 for example specifically refers to compositions which include components that are antibodies that bind to ST receptor, antibody fragments that bind to ST receptor and peptides that bind to ST receptor and which are non-peptide radiostable therapeutic agents. Each species within the scope of claim 23 shares these structural and functional features. Similarly, claim 42 specifically refers to liposomal compositions comprising a vesicle matrix wherein the ST receptor binding ligand is in the vesicle matrix and the active agent is inside the liposome in which the ST receptor binding ligand in the vesicle matrix is an antibody that binds to ST receptor, an antibody fragment that binds to ST receptor or a peptide that binds to ST receptor, and the active agent inside the liposome is a radiostable active agent. Each species within the scope of claim 42 shares these structural and functional features. In claim 48, the claim has been amended to recite that the compositions include components that are antibodies that bind to ST receptor, antibody fragments that bind to ST receptor and peptides that bind to ST receptor and which are non-peptide therapeutic agents or imaging agents. Each species within the scope of claim 23 shares these structural and functional features.

Regarding the assertion that the only examples of "pharmaceutical compositions" are disclosed in the specification are disclosed at pages 72-75, Applicants respectfully urge that such a conclusion is clearly erroneous. The specification is replete with specific examples of the claimed invention. In fact, Example 1 lists over eight hundred (800) individual and specific representative species, each of which fall within the scope of claim 23. Compound 2-D6 in Example 1 corresponds to an example of the elected species. In addition, the specification is replete with other examples of species according to the invention. Applicant has more than met the requirement for a sufficient description of a representative number of species as provided by the law.

Regarding the term "fragments" Applicant has further clarified the term to further refer to the function of binding to ST receptor. Thus, fragments clearly refer to only those molecules which have the specific activity of the full length version such that the must, as termed in the Office Action "exhibit the desired pharmaceutical effects"

Applicants respectfully urge that the grounds cited for rejecting the claims as failing to comply with the written description requirement are insufficient. The compositions are defined by common structural and functional features which are amply disclosed in the specification and exemplified by numerous representative species. Moreover, in no way do the grounds apply to the subject matter of claims 33, 34, 36, 38-40 and 44.

Applicant respectfully urges that the claims are in compliance with the written description requirement. Applicant respectfully requests that the rejection of claims 23, 25-28, 30-34, 36 and 38-56 under 35 U.S.C. §112, first paragraph, be withdrawn.

Enablement Rejection

Claims 23, 25-28, 30-34, 36 and 38-56 have been rejected under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement. The Official Action states on page 11 that

> the specification, while being enabling for use in isolated cells, does not reasonably provide enablement for pharmaceutical uses in animals or humans.

Initially, Applicant notes that the claim does not contain any reference or limitation with respect to intended use. If the Office finds that the claimed compositions are enabled, the rejection should be withdrawn without delay.

In asserting the claimed invention is not enabled by the specification, the analysis provided by the Office on pages 12-16 of the Official Action indicate that the primary grounds for the rejection turns on the alleged lack of predictability, whereby in view of the amount of guidance and absence of working examples provided by applicant, one skilled in the art would require undue experimentation to practice the invention. Applicant respectfully disagrees.

The invention relates to pharmaceutical compositions. The elements of the claims to the compositions of the invention include an ST receptor binding ligand, an active agent and a pharmaceutically acceptable carrier. Claims 42-47 additionally recite liposomes. The level of skill in the art is high. The application contains no *in vivo* data but does include numerous examples of embodiments and extensive discussion of how to make and use the invention.

The Office cites three references as evidence of the state of the art showing the practicing the claimed invention would be unpredictable and therefore the amount of experimentation required to practice the invention would amount to undue experimentation. The Office asserts that the state of the art of using peptides in highly unpredictable. The Office asserts that many problems exist in the use of peptides as drugs.

Cianfrocca et al (British Journal of Cancer, 2006, pp 1-6) is cited on page 13 as evidence that peptide drugs may be toxic. Applicant urges that Cianfrocca et al supports a finding of enablement. While the success observed by Cianfrocca et al was limited, nothing in the reference supports the conclusions that peptides cannot be used as drugs. The results in Cianfrocca et al support the opposite conclusion.

Russell-Jones (Journal of drug Targeting, 12(2):113-123 2004) is cited on page 13 as evidence that peptide drugs are not well suited for oral delivery. Applicant urges that Russell-Jones supports a finding of enablement. While Russell-Jones outlines problems with oral

delivery, the claims have no such limitation or requirement. In fact, claim 41 refers to injectable forms of the claimed compositions. More importantly, merely because peptides are not well suited for oral administration does not mean they can't be used. On the contrary, many drugs are delivered through other modes of delivery and the problems of peptides in oral routes, while an inconvenience to patients, does not diminish their uses as drugs. simply because "non-oral dosage forms are more difficult and traumatic to self administer than oral dosages" as stated on page 14 of the Official Action, does not in any way make peptide pharmaceuticals non-enabled.

El-Andaloussi et al. (Current Pharmaceutical Design, 11:3597-3611, 2005) is cited on page 13 as evidence that peptide drugs have delivery problems. The peptides in the present invention specifically bind to ST receptors. The problems outlined in El-Andaloussi et al. are not present in the present invention and on the contrary, are addressed by the invention. The problems discussed in El-Andaloussi et al. are specifically overcome by the nature of the invention. The citation of El-Andaloussi by the Office is misplaced because El-Andaloussi raises the question of peptides as drugs due to a problem of cell penetration. The peptides of the instant invention specifically bind to a receptor (ST receptor) on the cell membrane that is exposed to the outside of the cell. While El-Andaloussi raises the point of access by peptides to intracellular targets, the peptides in the invention bind to ST receptor, a cell membrane protein, not an intracellular protein. Applicant urges that El-Andaloussi et al. does not support a finding of non-enablement.

None of the references cited by the Office raise any specific issue of non-enablement. Cianfrocca et al. refers to toxicity and adverse effects which exist at some level in nearly every drug and nothing in Cianfrocca et al. suggests that peptide drugs are particularly ineffective due to toxicity problems. On the contrary, Cianfrocca et al. disclose that the peptide they were studying had some limited effectiveness. Although all the effectiveness was quite limited and disappointing, it was sufficient to establish some small benefit which , while perhaps not significant for commercial viability nonetheless meets the requirements of enablement for patentability. Russell-Jones refers to problems of oral administration of

peptide drugs. The present invention is not so limited and, in fact, some of the claims specifically require that the claims be injectable. Russell-Jones does not establish that peptides are not useful in pharmaceuticals, only that certain modes of administration are problematic. Accordingly, Russell-Jones does not establish that claimed invention lacks enablement. El-Andaloussi refers to problems of peptide drugs penetrating cells. The peptides used in the present invention are required to target proteins exposed to the outside of cells. The problems in El-Andaloussi are specifically avoided by the present invention. When all of the references are taken together, they do not raise sufficient questions to doubt the objective truth of Applicant's assertion of enablement. On the contrary, one skilled in the art would be more likely to accept the objective truth of Applicant's assertion of enablement in view of the cited references.

The claims are in compliance with the enablement requirement of the first paragraph of 35 U.S.C. §112. Applicant respectfully requests that the rejection of claims 23, 25-28, 30-34, 36 and 38-56 under 35 U.S.C. §112, first paragraph, as failing to comply with the enablement requirement be withdrawn.

Rejection under 35 U.S.C. §112, second paragraph

Claims 28, 30-34, 36 and 38-40 have been rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention.

Claim 28 has been canceled and claims 30-32, 36 and 39 have been amended to eliminate language lacking antecedent basis. The rejection is obviated by the amendment.

The claims as amended are clear and definite. Applicant respectfully requests that the rejection of claims 28, 30-34, 36 and 38-40 under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as his invention be withdrawn.

Rejection under 35 U.S.C. §103

Claim 42 have been rejected under 35 U.S.C. §103(a) as being unpatentable over Duflot et al. (U.S. Patent No. 4,499,080) in view of Goers et al. (U.S. Patent No. 4,867,973). Applicant respectfully disagrees. Applicant respectfully urges that the combination of references does not establish a prima facie case of obviousness. Duflot et al. teaches away from the invention and from a combination with Goers et al. One skilled in the art would not combine the references to produce the present invention.

Duflot et al. relates to vaccines which induce antibodies against the heat stable enterotoxin ST using synthetic peptides which do not have the structural conformation of active ST but which can induce antibodies that cross-react with ST. Duflot et al. does not disclose pharmaceutical compositions that comprise liposomes.

Goers et al teaches antibody-active agent conjugates. Goers et al. discloses compositions which include liposomes only passingly in the background section. The citation of Goers et al. appears to have been in error. Applicant respectfully urges that if the Office intended to use Goers et al. as the secondary citation, a prima facie case of obviousness has not been established. The combination of Duflot et al. with Goers et al does not yield the invention. The combination of Duflot et al. with Goers et al does not provide the elements of the claim.

The Official Action refers to "Gluck et a." on page 18, and makes specific reference to disclosure in the claims and specification of "Gluck et al." A review of the issued U.S. Patents listing an inventor named Gluck reveals one patent in particular, U.S. Patent No. 6,040,167, which includes disclosure corresponding to the commentary on page 18 of the Office Action. Applicant respectfully requests that the Office confirm that U.S. Patent No. 6,040,167, was the reference intended to be cited, not Goers, et al. Moreover, if U.S. Patent No. 6,040,167 was supposed to be the secondary reference of the obviousness rejection, Applicant respectfully requests that the U.S. Patent No. 6,040,167 be properly made of record. Gluck et al. discloses liposomes that include a fusion peptide that induces uptake by cells and a protein which binds to cell receptors.

It is asserted that it would have been prima facie obvious for one skilled in the art at the time the invention was made to use liposomes to deliver drugs. it is assereted that one skilled in the art would have been motivated to use liposomes to deliver drugs because doing so offers advantages of high permeability and low toxicity and that one skilled in the art would have a reasonable expectation of success because Gluck et al. teach utilization of liposomes with peptides and receptor binding proteins.

Applicant respectfully urges that the Office has not established a prima facie case of obviousness. Duflot et al. teaches away from the invention and from a combination with Gluck et al.. One skilled in the art would not combine the references to produce the present invention.

Duflot et al. teaches to conjugate its synthetic peptides with a non-toxic carrier protein so that the sequences which induce antibodies that cross-react with ST are immunogenic. The non-toxic carrier is intended to assist in presenting the peptide sequences in immunogenic form. Examples of the non-toxic carrier protein provided in the specification include pathogen toxins. In suggesting the use of pathogen toxins, Duflot et al indicate that the benefit of such choices is that the non-toxic carrier protein serves as an additional immunogenic target. Thus, the use of cholera toxin sequences or *Shigella* toxin serves the duel purpose of 1) assisting in presentation of the ST peptide sequences in immunogenic form to induce an immune response that will cross-react with ST as well as 2) serving as an immune target itself for inducing an immune response against the pathogen from which the toxin sequences were derived. In view of these teachings, one skilled in the art would not consider combining Duflot et al. with Gluck et al. to yield the present invention. One skilled in the art would not combine Duflot et al. with Gluck et al. to produce a liposome having a ST receptor binding ligand in the vesicle matrix and a radiostable active agent inside the liposome. The Office urges that the non-toxic carrier protein in Duflot et al. corresponds to the radiostable active agent of the present invention. Not only is the non-toxic carrier protein in Duflot et al. expressly non-toxic, its purpose is to serve as a immune target itself for inducing an immune response against the pathogen from which the toxin sequences were

derived. Therefore, one skilled in the art would not incorporate it within a liposome where it would be less effective as an immune target. One skilled in the art following the teachings of Duflot et al. would not seek to combine those teachings with Gluck et al. since the combination contradicts the teachings in Duflot et al. Duflot et al. teaches away form the combination and from the claimed invention.

Applicant respectfully urges that the combination of references does not establish a prima facie case of obviousness. Applicant respectfully urges that the subject matter of claim 42 is not obvious in view of the combination of Duflot et al. (U.S. Patent No. 4,499,080) in view of Goers et al. (U.S. Patent No. 4,867,973) or the combination of Duflot et al. (U.S. Patent No. 4,499,080) in view of Gluck et al. (U.S. Patent No. 6,040,167). Applicant respectfully requests that the rejection of claim 42 under 35 U.S.C. §103(a) as being unpatentable be withdrawn.

Double Patenting Rejections

Claims 23, 25-28, 33, 34, 38 and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 5 and 6 of U.S. Patent No. 5,962,220. Applicant will file appropriate terminal disclaimers upon indication that the pending claims would be otherwise allowable.

Claims 23, 25-28, 33, 34, 38 and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4, 7-10 and 13 of U.S. Patent No. 6,087,109. Applicant will file appropriate terminal disclaimers upon indication that the pending claims would be otherwise allowable.

Claims 23 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-24, 26, 28, 29 and 33-41 of U.S. Patent No. 7,097,839. Applicant will file appropriate terminal disclaimers upon indication that the pending claims would be otherwise allowable.

Claims 23, 25-28, 33, 34, 38, 40, 41, 42, 45 and 47 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2,

5, 6, 10 and 12 of U.S. Patent No. 5,962,220 in view of Goers et al. (U.S. Patent Number 4,867,973). As noted above, Goers et al. appears to be cited in error, as suggested by the later discussion of Gluck et al. in the rejection. The combination of claims 1, 2, 5, 6, 10 and 12 of U.S. Patent No. 5,962,220 and Goers et al. does not render the present invention obvious. The combination of claims 1, 2, 5, 6, 10 and 12 of U.S. Patent No. 5,962,220 and Gluck et al. does not render the present invention obvious. Applicant respectfully request clarification and withdrawal of the rejection of claims 23, 25-28, 33, 34, 38, 40, 41, 42, 45 and 47 under the judicially created doctrine of obviousness-type double patenting.

Claims 23 and 28 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6 and 8 of U.S. Patent No. 6,060,037. Applicant respectfully urges that the rejection of claim 23 and 28 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6 and 8 of U.S. Patent No. 6,060,037 is improper and respectfully requests reconsideration and withdrawal of the rejection.

In the Official Action dated October 1, 2004 in the instant application, a requirement for restriction was made. Seven separate and distinct groups of inventions were set forth in the restriction requirement and Applicant was required to elect one such invention for examination. Groups I and III were drawn to compositions. Groups II and IV-VII were drawn to methods. Applicant elected Group I.

Claims 1 and 2 of U.S. Patent No. 6,060,037 correspond non-elected Group IV of the instant application. Claim 6 of U.S. Patent No. 6,060,037 corresponds to non-elected Groups II and V of the instant application. Claim 8 of U.S. Patent No. 6,060,037 corresponds to non-elected Group VI and of the instant application.

Thus, each of claims 1, 2, 6 and 8 of U.S. Patent No. 6,060,037 refer to subject matter which was deemed as separate and distinct inventions from the subject matter of the claims in the instant application. A finding that the claims are obvious in view of the cited claims is completely contrary and inconsistent with the position taken by the Office in requiring restriction.

Applicant respectfully requests withdrawal of the rejection of claims 23 and 28 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2, 6 and 8 of U.S. Patent No. 6,060,037.

Conclusion

Claims 23, 25-27, 30-34, 36, 38-48 and 50-58 are in allowable form. An indication of allowability is therefore earnestly solicited. Applicant invites the Examiner to contact the undersigned at 215-665-5592 to clarify any unresolved issues raised by this response.

As indicated on the transmittal accompanying this response, the Commissioner is hereby authorized to charge any debit or credit any overpayment to Deposit Account No. 50-1275.

Respectfully submitted,

Date: February 27, 2007

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